



NOTES

PURINE & PYRIMIDINE METABOLISM DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Enzymatic disorders in biochemical pathways crucial for biosynthesis of nucleobases → impaired nucleotide formation
 - Adenosine triphosphate (ATP), guanosine monophosphate (GMP)
- Inherited conditions

SIGNS & SYMPTOMS

- Disease-specific
- Lesch–Nyhan syndrome
 - Kidney stones, hematuria, urinary tract infections (UTIs), arthritis, tophi
 - Spasticity, chorea, hyperactive reflexes, grimacing, dystonia
 - Intellectual impairment, developmental delay, self mutilation, lack of speech, compulsions
- Orotic aciduria
 - Glossitis, growth failure, developmental delay, intellectual disability, congenital malformation, immunodeficiency

DIAGNOSIS

LAB RESULTS

- No activity in one enzyme, excess in one metabolite

OTHER DIAGNOSTICS

- Clinical evaluation, genetic testing

TREATMENT

MEDICATIONS

- Lesch–Nyhan syndrome
 - Xanthine oxidase inhibitors, benzodiazepines, baclofen, gabapentin, neuroleptics

OTHER INTERVENTIONS

- Lesch–Nyhan syndrome
 - Lithotripsy, protecting devices
- Orotic aciduria
 - Pyrimidine replacement therapy

VISIT...

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LESCH–NYHAN SYNDROME

osms.it/lesch-nyhan_syndrome

PATHOLOGY & CAUSES

- Rare disease; excess of uric acid

CAUSES

- X-linked recessive mutation in *HPRT* gene → lack of enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
- Decreased HGPRT activity, recycling of cell waste products → increased transformation of cell waste products into uric acid → increased uric acid

COMPLICATIONS

- Uric acid precipitation in urine → urate stones in kidney, ureter, bladder → renal failure
- Uric acid deposition in joints → gout-like arthritis (AKA juvenile gout)
- Central nervous system (CNS) alterations, may be due to
 - Uric acid accumulation → oxidative damages
 - Decreased nucleotide production → decreased dopamine production → lesions in striatal dopaminergic pathways
- Insufficient vitamin B₁₂ → megaloblastic anemia

SIGNS & SYMPTOMS

- Uric acid hyperproduction
 - Urate precipitation in urinary tract: “orange sand” deposits in diapers of infants; kidney stones → hematuria, UTIs
 - Arthritis, tophi
- Neuromuscular
 - Spasticity, chorea, hyperactive reflexes, grimacing, dystonia

- Behavioural, cognitive
 - Intellectual impairment, developmental delay, self-mutilation (e.g. finger, lip biting), lack of speech, compulsions (e.g. spitting)

DIAGNOSIS

LAB RESULTS

- HGPRT activity in blood, other tissues
- Increased urate-to-creatinine ratio in urine
- Hyperuricosuria, hyperuricemia

OTHER DIAGNOSTICS

- Clinical evaluation, genetic testing

TREATMENT

MEDICATIONS

- Xanthine oxidase inhibitors to reduce production of uric acid
- Benzodiazepines, baclofen for neurological issues
- Benzodiazepines, gabapentin, neuroleptics for behavioural issues

OTHER INTERVENTIONS

- Lithotripsy for kidney stones
- Protecting devices for behavioural issues

OROTIC ACIDURIA

osms.it/orotic-aciduria

PATHOLOGY & CAUSES

- Extremely rare disease; alteration in pyrimidine synthesis → **excessive** excretion of **orotic acid** (intermediate metabolite) in urine

CAUSES

- **Autosomal recessive** disease
- **Defect in** activity of uridine monophosphate synthetase (**UMPS**) → decreased UTP production and increased dihydroorotate accumulation
 - **Type 1:** both enzymes affected; orotidine monophosphate decarboxylase (OMP-decarboxylase), orotate phosphoribosyltransferase (OPRT)
 - **Type 2:** only OMP-decarboxylase affected

COMPLICATIONS

- Decreased production of pyrimidin, cofactors needed for erythropoiesis → **megaloblastic anemia unresponsive to vitamin B₁₂ supplementation, folic acid**

SIGNS & SYMPTOMS

- Glossitis
- **Growth failure**
- **Developmental delay**
- Intellectual disability
- Congenital malformation
- Immunodeficiency

DIAGNOSIS

LAB RESULTS

- Anemia
- Orotic acid dosage in urine

OTHER DIAGNOSTICS

- Clinical evaluation

TREATMENT

OTHER INTERVENTIONS

- Pyrimidine replacement therapy
 - **Uridine monophosphate**